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Monitoring system for substandard detection of antituberculosis drugs used in the Mauritanian National Health System

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1. Introduction

Global sales of medicines have risen from US$ 500 billion to US$ 1.1 trillion in 15 years. This growth it is related with the inclusion of substandard and falsified medicines in the pharmaceutical market. These medicines can prolong illness, promote drug-resistant infections or could make people die because of being untreated or killed by the product itself [1].

From 2013 to 2017, 1450 reports were received by The World Health Global Surveillance and Monitoring System, being 42% from the African region. The highest percentage of all products reported belongs to medicines to treat malaria and antibiotics, 19.6 and 16.9% respectively [1].

Nowadays it is not possible to know the absolute number of substandard and falsified medical products worldwide as the notifications comes from the national or regional medicines regulatory authorities and they need to be trained to identify and report incidents. However, it is not always possible to have the possibility of having a laboratory accredited by the World Health Organization (WHO) for the detection of substandard and falsified drugs [1].

Faced with this situation, the ISACAM project arises to develop a system that ensures the quality of drugs used in the treatment of tuberculosis (TB), AIDS and Malaria, in collaboration with the Laboratoire National de Contrôle de la Qualité des Médicaments in Mauritania (LNCQM). In addition, another objective is to collaborate so that the LNCQM achieves the accreditation of the WHO as a reference laboratory in the country for the detection of substandard and falsified drugs.

The objective of this work was to analyze the quality of antiTB drugs used in the Mauritanian National Health System.

2. Materials and methods

13 medicines to treat TB with isoniazid (INH), pyrazinamide (PZA), rifampicin (RFP), ethambutol (EMB) and levofloxacine (LVFX) as active pharmaceutical ingredients (APIs) were collected from different locations at Nouakchott (Islamic Republic of Mauritania). The

preparations were collected from distribution offices and programs such as "The National Program against TB and Leprosi" (PNLTL) but also from diagnostic and treatment centers (DTC).

In each sampling area an identification card was filled for each medicine with information related to packaging (lot, number of units, expiry date, manufacturer laboratory and packaging conditions), storage place (type of establishment, name, storage conditions), person responsible for sampling and date. Then, the product was placed in an isothermal bag and transported to ULL lab, where it was storage at 5 ºC and 11 % of relative humidity.

Every medicine was analyzed testing their mass uniformity, content uniformity, disintegration time and dissolution according to European Pharmacopoeia. Drug content was analyzed by chromatography using an Acquity UPLC® H-Class System with analytical methods previously validated. In the case of the dissolution test, medium, apparatus and rotation speed were selected according to the monograph published for each drug by the United States Pharmacopoeia. Friability was performed if indicated.

3. Results and Discussion

As of today, 10 medicines have been completely analyzed. All products complied with mass uniformity and disintegration test. However, problems related to tablet friability, drug content and dissolution were found for some of them, see table 1.

The products with PZA (l16TPF030 and NPB919A) did not comply with the recommendations as tablets were cracked during friability test. In the case of fixed dose combination of INH and RFP (NRH9392A), this medicine did not fulfil with API content, independently of sampling site. Then, the problem might be located in the laboratory of manufacture. This agrees with previously published studies from other African countries which also detected problems with these combinations of APIs [2].

The product which combines 3 APIs (S46) did not comply with dissolution test as RFP release was below limit. In this case must be indicated the bad conditions of the packaging and the proximity of expiration date.

4. Conclusions

At the moment 60 % of the antiTB drug included in the present study were considered

Table 1. Results for quality control. IBN: Centre de santé de Araffat Ibn Sina

APIs	Lot	Sampling site	Acceptance value	Dissolution (% of drug release)
LVFX	E2M103	PNLTL	2.20	81.1 ± 2.8 (n=12)
PZA	16TPF030	PNLTL	9.20	95.6 ± 1.1 (n=6)
PZA	NPB919A	IBN	5.30	94.8 ± 2.4 (n=6)
EMB EMB	EEZ643 EEZ923D	PNLTL Polyclinique	4.40 4.60	100.3 ± 4.4 (n=6) 97.5 ± 0.7 (n=6)
INH + RFP	NRH9352A	DTC	INH: 15.0 RFP: 11.3	INH: 97.4 ± 5.4 (n=12) RFP: 78.8 ± 7.1 (n=12)
INH + RFP	NRH9352A	Polyclinique	INH: 13.0 RFP: 19.0	INH: 98.3 ± 6.3 (n=6) RFP: 90.4 ± 7.2 (n=6)
INH + RFP	NRH9352A	IBN	INH: 18.0 RFP: 13.0	INH: 102.0 ± 3.0 (n=12) RFP: 92.8 ± 8.8 (n=12)
INH + RFP + PZA	S46	IBN	INH: 11.4 RFP: 15.1 PZA: 7.45	INH: 93.0 ± 7.0 (n=6) RFP: 29.0 ± 21.7 (n=6) PZA: 99.0 ± 2.7 (n=6)
INH + RFP + PZA + EMB	NRG69208	DTC	INH: 10.3 RFP: 10.1 PZA: 4.5 EMB 5.4	INH: 102.3 ± 2.1 (n=6) RFP: 95.3 ± 3.2 (n=6) PZA: 104.8 ± 3.0 (n=6) EMB: 101.7 ± 2.4 (n=6)

as substandard being the variability of API content the most frequent problem. Although, all the techniques and procedures used were documented and transferred to the LNCQM, it is necessary to increase the means, training, and qualification of the personnel of this Lab to be able to achieve the objectives of the WHO regarding the detection of substandard or falsified medicines.

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